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2

As such, 37 CFR 1.475, which corresponds to PCT Rule 13, should be followed when considering such issues. As stated in MPEP 1893.03 (d):

Examiners are reminded that unity of invention (not restriction) practice is applicable in international applications (both Chapter I and II) and in national stage applications submitted under 35 U.S.C. 371.

In this regard, the Office Action comments that the inventions listed as Groups I-X and the species noted above do not comply with the criteria under PCT Rule 13.1. However, during the international phase of the corresponding PCT application, the PCT International authorities did not raise any such issues. This is evidenced by the Written Opinion and the International Preliminary Report on Patentability (copies attached), which issued in the PCT case, which in both cases did not present any indications under "Box No. IV". This inconsistency thus indicates that the relevant PCT criteria have not been applied in the instant national phase application.

Further, Applicants respectfully submit that the Office Action has failed to establish that a search of the complete application would be an undue burden as required by MPEP 803. It is Applicants' position that the Office Action has failed to establish that a search of the entire application constitutes an undue burden.

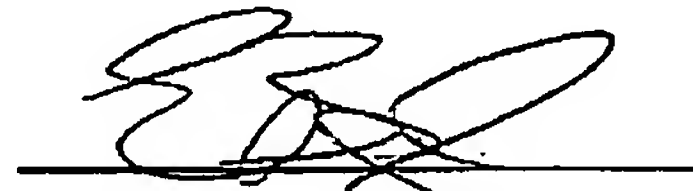
The present election is made without prejudice or disclaimer as to any non-elected subject matter. Applicant specifically reserves the right to file one or more divisional application(s) directed to non-elected subject matter.

In light of the foregoing response, all the outstanding objections and rejections are considered overcome. Applicant respectfully submits that this application should now be in condition for allowance and respectfully requests favorable consideration.

Respectfully submitted,

March 9, 2009

Date



Attorney for Applicant
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Reg. No. 57,542

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 85409-29	FOR FURTHER ACTION See item 4 below	
International application No. PCT/CA2004/000726	International filing date (day/month/year) 14 May 2004 (14.05.2004)	Priority date (day/month/year) 16 May 2003 (16.05.2003)
International Patent Classification (IPC) or national classification and IPC A61P 25/00, 23/00, A61K 39/395, 31/00, G01N 33/48		
Applicant UNIVERSITE LAVAL		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).	
2.	This REPORT consists of a total of 11 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.	
3.	This report contains indications relating to the following items:	
	<input checked="" type="checkbox"/> Box No. I	Basis of the report
	<input checked="" type="checkbox"/> Box No. II	Priority
	<input checked="" type="checkbox"/> Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
	<input type="checkbox"/> Box No. IV	Lack of unity of invention
	<input checked="" type="checkbox"/> Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
	<input checked="" type="checkbox"/> Box No. VI	Certain documents cited
	<input type="checkbox"/> Box No. VII	Certain defects in the international application
	<input type="checkbox"/> Box No. VIII	Certain observations on the international application
4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).	

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Date of issuance of this report 18 November 2005 (18.11.2005)
	Authorized officer Athina Nickitas-Etienne Telephone No. +41 22 338 89 95

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)Applicant's or agent's file reference
see form PCT/ISA/220FOR FURTHER ACTION
See paragraph 2 belowInternational application No.
PCT/CA2004/000726International filing date (day/month/year)
14.05.2004Priority date (day/month/year)
16.05.2003International Patent Classification (IPC) or both national classification and IPC
A61P25/00, A61P23/00, A61K39/395, A61K31/00, G01N33/48Applicant
UNIVERSITE LAVAL

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for International preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b(s)(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Irion, A

Telephone No. +49 89 2399-8174



Form PCT/ISA/237 (Cover Sheet) (January 2004)

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/CA2004/000726**Box No. I Basis of the opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☒ in written format
☒ in computer readable form
 - c. time of filing/furnishing:
☒ contained in the international application as filed.
☒ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/CA2004/000726

Box No. II Priority

1. ☒ The following document has not been furnished:☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/CA2004/000726**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial
applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-21,31,33,35-43,53-81(IA);1-15,17,19,21-38,40,42,53-58,60,62,64,81 (all partially; N,IE,IA)

because:

- ☒ the said international application, or the said claims Nos. 1-21,31,33,35-43,53-81 (IA) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-15,17,19,21-38,40,42,53-58,60,62,64,81 (all partially)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- the written form ☐ has not been furnished
- ☐ does not comply with the standard
- the computer readable form ☐ has not been furnished
- ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/CA2004/000726**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement****1. Statement**

Novelty (N)	Yes: Claims	44-52, 65-81
	No: Claims	1-43, 53-64
Inventive step (IS)	Yes: Claims	44-52, 65-81
	No: Claims	1-43, 53-84
Industrial applicability (IA)	Yes: Claims	22-30, 32, 34, 44-52
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited**1. Certain published documents (Rules 43bis.1 and 70.10)**

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/CA2004/000726

Item III**III.1 With respect to claims 1-15, 17, 19, 21-38, 40, 42, 53-58, 60, 62, 64, and 81**

Claims 1-15, 17, 19, 21-38, 40, 42, 53-58, 60, 62, 64, and 81 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved,

1. decreasing an intracellular chloride level (claims 1, 11, 22, 27, 33, 34, 53, 81)
2. modulating the activity or expression of a chloride transporter (claims 2, 12, 23, 28, 35, 54)
3. increasing the KCC2 activity or expression (claims 4, 14, 25, 30, 37, 56, 57)
4. inhibiting the TrkB (claims 15, 38, 58)
5. inhibiting the PKA (claims 17, 40, 57) or
6. inhibiting the CAM kinase (claims 19, 42, 62)

which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. Although the effects can be measured, the skilled person is not in the position without undue burden to screen all known and even yet to be discovered compounds used for the treatment of pain as to their effect on intracellular chloride levels.

This afore mentioned defect is such that it has not been possible to carry out a meaningful search on the whole subject-matter. Thus the search, and therefore the examination has been limited to compounds explicitly disclosed in the application. However, in view of large number thereof and of the lack of any structural feature common to all of these compounds the search could not be limited to all of them (Article 6 PCT, lack of conciseness). Moreover, for the compounds disclosed on p. 24 l. 15-22, no data are provided as to their effect on chloride levels in neuronal cells (Article 6 PCT, lack of support). Hence the search, and therefore the examination have been limited to the following compounds:

- (i) inhibitor of TrkB: K-252a, anti-TrkB antibodies, N-ethylmaleimide, staurosporine as disclosed in claims 16, 39, 59, and p. 23 l. 14-32
 - (ii) inhibitor of PKA: H-89 as disclosed in claims 18, 41, 61, and p. 23 l. 32 - p. 24 l. 4
 - (iii) inhibitor of CAM kinase: KN-93 as disclosed in claims 20, 43, 63, and p. 24 l. 4-10
 - (iv) anti-sense KCC2 mRNA as disclosed in the Example 2 of the application.
- The compounds (i), (ii), and (iii) are disclosed further on p. 3 l. 25-31, p. 5 l. 10-17,

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/CA2004/000726

p. 7 l. 17-24, Examples 2-4).

III.2 With respect to claims 1-21, 31, 33, 35-43, and 53-81

Claims 1-21, 31, 33, 35-43, and 53-81 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(I) PCT).

Item V**V.1 Reference is made to following documents**

- D1: US2002028779 (HIGH ET AL.) 07 March 2002 (2002-03-07)
- D2: WO02102232 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 27 December 2002 (2002-12-27)
- D3: K.O. ALEY & J.D. LEVINE: 'Role of protein kinase A in the maintenance of inflammatory pain', THE JOURNAL OF NEUROSCIENCE, 15 March 1999 (1999-03-15), vol. 19, no. 6, pages 2181-2186
- D4: X.Y. HUA ET AL.: 'Inhibition of spinal protein kinase C reduces nerve injury-induced tactile allodynia in neuropathic rats', NEUROSCIENCE LETTERS, 1999, vol. 276, pages 99-102
- D5: L. FANG ET AL.: 'CaMK II signaling in central sensitization in a rat model of visceral pain', SOCIETY FOR NEUROSCIENCE ABSTRACTS, 2001, vol. 27, no. 2, page 2163 & 31st Annual Meeting of the Society for Neuroscience, San Diego, California, USA; November 10-15, 2001
- D6: US2004032870 (RINAT NEUROSCIENCE CORP) 22 April 2004 (2004-04-22)
- D7: J.A.M. COULL ET AL.: 'Trans-synaptic shift in anion gradient in spinal lamina I neurons as a mechanism of neuropathic pain', NATURE, 21 August 2003 (2003-08-21), vol. 424, pages 938-942

V.2 Novelty (Article 33(2) PCT)**V.2.1 With respect to claims 1-16, 21-39, 53-59, and 64**

Document D1 describes the treatment of pain using the Trk inhibitor K-252a (paragraph [0010]-[0012], [0023], [0028]-[0029], [0041],[0050]-[0051]; Example 2; claims 2, 12, 19). Therefore, the subject-matter of claims 1-16, 21-39, 53-59 and 64

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/CA2004/000726

is not considered novel in the sense of Article 33(2) PCT, since a newly identified mode of action, which is in the present case decreasing the intracellular chloride level, is not a feature which confers novelty on a medical use.

V.2.2 With respect to claims 1-13, 17, 18, 21-37, 40, 41, 53-57, 60, 61, and 64

Document D2 describes the use of the PKA inhibitor H-89 in combination with inhibitors of the Ras-MEK-ERK cascade for the treatment of pain, e.g. hyperalgesia, neuropathic pain and inflammatory pain (p. 7 l. 4-8, p. 3 l. 1-2, p. 10 l. 20-23, p. 14 l. 7-9, claim 94, p. 56 l. 17-20). Furthermore, D2 describes production of hyperalgesia through the activation of PKA (p. 41 l. 15-28) and document D3 describes the use of PKA inhibitors for the reduction of hyperalgesia (abstract).

Document D4 describes the use of H-89 having anti-allodynic activity (abstract).

Therefore, the subject-matter of claims 1-13, 17, 18, 21-37, 40, 41, 53-57, 60, 61, and 64 is not considered novel in the sense of Article 33(2) PCT.

V.2.3 With respect to claims 1-7, 9, 11-13, 19-37, 42, 43, 53-57, and 62-64

Document D5 describes the use of KN-93 for the treatment of visceral pain (abstract).

Therefore, the subject-matter of claims 1-7, 9, 11-13, 19-37, 42, 43, 53-57, and 62-64 is not considered novel in the sense of Article 33(2) PCT.

V.2.4 With respect to claims 44-52, and 65-81

None of the documents cited in the international search report describe a method of identifying or characterizing a compound for the treatment or prevention of pain comprising the determination of the intracellular chloride level and a method for diagnosing or prognosticating pain associated with CNS dysfunction comprising the determination of the intracellular chloride level. Therefore, the subject-matter of claims 44-52 and 65-81 is considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)**V.3.1 With respect to claims 44-52 and 65-81**

None of the documents cited in the international search report suggest that the determination of the intracellular chloride level might be the basis of the identification of compounds being beneficial in pain treatment or diagnosis. Therefore, the subject-matter of claims 44-52 and 65-81 is considered inventive in the sense of Article 33(3) PCT.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/CA2004/000726**V.4 Industrial applicability (Article 33(4) PCT)****V.4.1 With respect to claims 1-23 and 25**

The subject-matter of claims 22-30, 32, 34, 44-52 appears to be susceptible of industrial application.

V.4.2 With respect to claims 1-21, 31, 33, 35-43, 53-81

The subject-matter of claims 1-21, 31, 33, 35-43, 53-81 is considered to be a method of treatment by therapy of the human or animal body and/or a diagnostic method practised on the human/animal body.

For the assessment of the present claims 1-21, 31, 33, 35-43, 53-81 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.5 Further remarks**V.5.1 With respect to claim 3**

The abbreviation "KCC2" used in the claims should be spelled out at least once, e.g. in claim 3, in order to avoid a lack of clarity (Article 6 PCT).

V.5.2 With respect to claims 21 and 64

The term "substantially identical" used in claims 21 and 64 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

Item VI**VI.1 With respect to documents D6-D7**

The examination report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the above cited

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/CA2004/000726

documents D6-D7 would be relevant with respect to novelty and inventive step (Article 33(2) and (3) PCT). Furthermore, should the present application be entered into the regional phase, the document D6 could be relevant to the question of novelty.

PATENT COOPERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

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To:

SMART
1000 de la Gauchetière Ouest
Suite 3400
Montreal, Quebec H3B 4W5
CANADA

1000 DE LA GAUCHETIÈRE OUEST

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

08/10/2004

Applicant's or agent's file reference

85409-29

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/CA2004/000726

International filing date
(day/month/year)

14/05/2004

Applicant

UNIVERSITE LAVAL

ON
DOCKET

Info TBF USIAU → Jan 8.2005

Amend out 19 → Dec 8.2004.

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
 - ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Catriona Cleere

Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)".

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 85409-29	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/CA2004/000726	International filing date (day/month/year) 14/05/2004	(Earliest) Priority Date (day/month/year) 16/05/2003
Applicant UNIVERSITE LAVAL		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☒ With regard to any nucleotide or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box II).

3. ☐ Unity of invention is lacking (see Box III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. 1

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

Form PCT/ISA/210 (first sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.

CT/CA2004/000726

Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
- a. type of material
- ☒ a sequence listing
- ☐ table(s) related to the sequence listing
- b. format of material
- ☒ in written format
- ☒ in computer readable form
- c. time of filing/furnishing
- ☒ contained in the international application as filed
- ☒ filed together with the international application in computer readable form
- ☐ furnished subsequently to this Authority for the purpose of search
2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

Form PCT/ISA/210 (continuation of first sheet (1)) (January 2004)

PCT/CA2004/000726

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61P25/00 A61P23/00 A61K39/395 A61K31/00 G01N33/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, MEDLINE, EMBASE, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>→ US 2002/028779 A1 (HIGH KARIN WESTLUND ET AL) 7 March 2002 (2002-03-07)</p> <p>paragraph '0010! - paragraph '0012! paragraph '0023! paragraph '0028! - paragraph '0029! paragraph '0041! paragraph '0050! - paragraph '0051: example 2 claims 4,12,19</p> <p style="text-align: center;">-/-</p>	<p>1-16, 21-39, 53-59,64</p>

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

23 September 2004

Date of mailing of the international search report

08/10/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2
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Fax (+31-70) 340-3016

Authorized officer

Irion, A

Form PCT/ISA/210 (second sheet) (January 2004)

PCT/CA2004/000726

C.(Continuation) DOCUMENTS CONSULTED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>✓ WO 02/102232 A (UNIV CALIFORNIA ; LEVINE JON DAVID (US); MESSING ROBERT O (US)) 27 December 2002 (2002-12-27)</p> <p>page 7, line 4 - line 8 page 3, line 1 - line 2 page 10, line 20 - line 23 page 14, line 7 - line 9 page 56, line 17 - line 20 claim 94</p>	1-13,17, 18, 21-37, 40,41, 53-57, 60,61,64
X	<p>✓ ALEY KOCHUVELIKAKAM O ET AL: "Role of protein kinase A in the maintenance of inflammatory pain" JOURNAL OF NEUROSCIENCE, vol. 19, no. 6, 15 March 1999 (1999-03-15), pages 2181-2186, XP002297725 ISSN: 0270-6474 abstract</p>	1-13,17, 18, 21-37, 40,41, 53-57, 60,61,64
X	<p>✓ HUA XIAO-YING ET AL: "Inhibition of spinal protein kinase C reduces nerve injury-induced tactile allodynia in neuropathic rats" NEUROSCIENCE LETTERS, vol. 276, no. 2, 3 December 1999 (1999-12-03), pages 99-102, XP002297726 ISSN: 0304-3940 abstract</p>	1-13,17, 18, 21-37, 40,41, 53-57, 60,61,64
X	<p>✓ DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 2001, FANG L ET AL: "CaMK II signaling in central sensitization in a rat model of visceral pain" XP002297727 Database accession no. PREV200200002912 abstract & SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 27, no. 2, 2001, page 2163, 31ST ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE; SAN DIEGO, CALIFORNIA, USA; NOVEMBER 10-15, 2001 ISSN: 0190-5295</p>	1-7,9, 11-13, 19-37, 42,43, 53-57, 62-64

-/-

PCT/CA2004/000726

C.(Continuation) DOCUMENTS CONSIL D TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	✓ WO 2004/032870 A (RINAT NEUROSCIENCE CORP ; SHELTON DAVID L (US); VERGARA GERMAN J (US)) 22 April 2004 (2004-04-22) paragraph '0042!; figure 9 paragraph '0128! paragraph '0185!; example 5	1-16, 21-39, 53-59,64
P, X	✓ COULL JEFFREY A M ET AL: "Trans-synaptic shift in anion gradient in spinal lamina I neurons as a mechanism of neuropathic pain." NATURE (LONDON), vol. 424, no. 6951, 21 August 2003 (2003-08-21), pages 938-942, XP002294556 ISSN: 0028-0836 the whole document	44-52, 65-81
P, A		1-43, 53-64
A	✓ WO 93/00909 A (REGENERON PHARMA) 21 January 1993 (1993-01-21) the whole document	1-16, 21-39, 53-59,64
A	✓ WO 01/85151 A (RAYCHAUDHURI SIBA P ; RAYCHAUDHURI SMRITI K (US); FARBER EUGENE M (US)) 15 November 2001 (2001-11-15) the whole document	1-16, 21-39, 53-59,64
A	✓ DE PLATER G M ET AL: "Venom from the platypus, Ornithorhynchus anatinus, induces a calcium-dependent current in cultured dorsal root ganglion cells" JOURNAL OF NEUROPHYSIOLOGY (BETHESDA), vol. 85, no. 3, March 2001 (2001-03), pages 1340-1345, XP002294557 ISSN: 0022-3077 the whole document	1-16, 21-39, 53-59,64

International Application No. PCT/CA2004/000726

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 1-21,31,33,35-43,53-81 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 65-81 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2004/000726**Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-21, 31, 33, 35-43, 53-81 (all partially)
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)

Information on patent family members

PCT/CA2004/000726

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
→ US 2002028779 A1	07-03-2002	NONE	
✓ WO 02102232 A	27-12-2002	WO 02102232 A2 US 2003008807 A1	27-12-2002 09-01-2003
✓ WO 2004032870 A	22-04-2004	WO 2004032870 A2	22-04-2004
✓ WO 9300909 A	21-01-1993	AU 2322392 A CA 2112799 A1 EP 0593663 A1 IE 921315 A1 JP 6509333 T NZ 242467 A PT 100424 A WO 9300909 A1 ZA 9202946 A	11-02-1993 21-01-1993 27-04-1994 13-01-1993 20-10-1994 27-06-1995 29-10-1993 21-01-1993 30-12-1992
✓ WO 0185151 A	15-11-2001	AU 6132401 A WO 0185151 A2	20-11-2001 15-11-2001

Form PCT/ISA/210 (patent family annex) (January 2004)

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From the
INTERNATIONAL SEARCHING AUTHORITY

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To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)Applicant's or agent's file reference
see form PCT/ISA/220**FOR FURTHER ACTION**
See paragraph 2 belowInternational application No.
PCT/CA2004/000726International filing date (day/month/year)
14.05.2004Priority date (day/month/year)
16.05.2003International Patent Classification (IPC) or both national classification and IPC
A61P25/00, A61P23/00, A61K39/395, A61K31/00, G01N33/48Applicant
UNIVERSITE LAVAL

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
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Authorized Officer

Irion, A

Telephone No. +49 89 2399-8174



Form PCT/ISA/237 (Cover Sheet) (January 2004)

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/CA2004/000726**Box No. 1 Basis of the opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☒ in written format
☒ in computer readable form
 - c. time of filing/furnishing:
☒ contained in the international application as filed.
☒ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF T.
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/CA2004/000726

Box No. II Priority

1. ☒ The following document has not been furnished:☒ copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).☐ translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/CA2004/000726

Item III**III.1 With respect to claims 1-15, 17, 19, 21-38, 40, 42, 53-58, 60, 62, 64, and 81**

Claims 1-15, 17, 19, 21-38, 40, 42, 53-58, 60, 62, 64, and 81 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved,

1. decreasing an intracellular chloride level (claims 1, 11, 22, 27, 33, 34, 53, 81)
2. modulating the activity or expression of a chloride transporter (claims 2, 12, 23, 28, 35, 54)
3. increasing the KCC2 activity or expression (claims 4, 14, 25, 30, 37, 56, 57)
4. inhibiting the TrkB (claims 15, 38, 58)
5. inhibiting the PKA (claims 17, 40, 57) or
6. inhibiting the CAM kinase (claims 19, 42, 62)

which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. Although the effects can be measured, the skilled person is not in the position without undue burden to screen all known and even yet to be discovered compounds used for the treatment of pain as to their effect on intracellular chloride levels.

This afore mentioned defect is such that it has not been possible to carry out a meaningful search on the whole subject-matter. Thus the search, and therefore the examination has been limited to compounds explicitly disclosed in the application. However, in view of large number thereof and of the lack of any structural feature common to all of these compounds the search could not be limited to all of them (Article 6 PCT, lack of conciseness). Moreover, for the compounds disclosed on p. 24 l. 15-22, no data are provided as to their effect on chloride levels in neuronal cells (Article 6 PCT, lack of support). Hence the search, and therefore the examination have been limited to the following compounds:

- (i) inhibitor of TrkB: K-252a, anti-TrkB antibodies, N-ethylmaleimide, staurosporine as disclosed in claims 16, 39, 59, and p. 23 l. 14-32
 - (ii) inhibitor of PKA: H-89 as disclosed in claims 18, 41, 61, and p. 23 l. 32 - p. 24 l. 4
 - (iii) inhibitor of CAM kinase: KN-93 as disclosed in claims 20, 43, 63, and p. 24 l. 4-10
 - (iv) anti-sense KCC2 mRNA as disclosed in the Example 2 of the application.
- The compounds (i), (ii), and (iii) are disclosed further on p. 3 l. 25-31, p. 5 l. 10-17,

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/CA2004/000726

p. 7 l. 17-24, Examples 2-4).

III.2 With respect to claims 1-21, 31, 33, 35-43, and 53-81

Claims 1-21, 31, 33, 35-43, and 53-81 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(I) PCT).

Item V**V.1 Reference is made to following documents**

- D1: US2002028779 (HIGH ET AL.) 07 March 2002 (2002-03-07)
- ↓ D2: WO02102232 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 27 December 2002 (2002-12-27)
- ✓ D3: K.O. A' EY & J.D. LEVINE: 'Role of protein kinase A in the maintenance of inflammatory pain', THE JOURNAL OF NEUROSCIENCE, 15 March 1999 (1999-03-15), vol. 19, no. 6, pages 2181-2186
- ↓ D4: X.Y. HUA ET AL.: 'Inhibition of spinal protein kinase C reduces nerve injury-induced tactile allodynia in neuropathic rats', NEUROSCIENCE LETTERS, 1999, vol. 276, pages 99-102
- ↓ D5: L. FANG ET AL.: 'CaMK II signaling in central sensitization in a rat model of visceral pain', SOCIETY FOR NEUROSCIENCE ABSTRACTS, 2001, vol. 27, no. 2, page 2163 & 31st Annual Meeting of the Society for Neuroscience, San Diego, California, USA; November 10-15, 2001
- D6: US2004032870 (RINAT NEUROSCIENCE CORP) 22 April 2004 (2004-04-22)
- ↓ D7: J.A.M. COULL ET AL.: 'Trans-synaptic shift in anion gradient in spinal lamina I neurons as a mechanism of neuropathic pain', NATURE, 21 August 2003 (2003-08-21), vol. 424, pages 938-942

V.2 Novelty (Article 33(2) PCT)**V.2.1 With respect to claims 1-16, 21-39, 53-59, and 64**

Document D1 describes the treatment of pain using the Trk inhibitor K-252a (paragraph [0010]-[0012], [0023], [0028]-[0029], [0041], [0050]-[0051]; Example 2; claims 2, 12, 19). Therefore, the subject-matter of claims 1-16, 21-39, 53-59 and 64

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/CA2004/000726

is not considered novel in the sense of Article 33(2) PCT, since a newly identified mode of action, which is in the present case decreasing the intracellular chloride level, is not a feature which confers novelty on a medical use.

V.2.2 With respect to claims 1-13, 17, 18, 21-37, 40, 41, 53-57, 60, 61, and 64

Document D2 describes the use of the PKA inhibitor H-89 in combination with inhibitors of the Ras-MEK-ERK cascade for the treatment of pain, e.g. hyperalgesia, neuropathic pain and inflammatory pain (p. 7 l. 4-8, p. 3 l. 1-2, p. 10 l. 20-23, p. 14 l. 7-9, claim 94, p. 56 l. 17-20). Furthermore, D2 describes production of hyperalgesia through the activation of PKA (p. 41 l. 15-28) and document D3 describes the use of PKA inhibitors for the reduction of hyperalgesia (abstract).

Document D4 describes the use of H-89 having anti-allodynic activity (abstract).

Therefore, the subject-matter of claims 1-13, 17, 18, 21-37, 40, 41, 53-57, 60, 61, and 64 is not considered novel in the sense of Article 33(2) PCT.

V.2.3 With respect to claims 1-7, 9, 11-13, 19-37, 42, 43, 53-57, and 62-64

Document D5 describes the use of KN-93 for the treatment of visceral pain (abstract).

Therefore, the subject-matter of claims 1-7, 9, 11-13, 19-37, 42, 43, 53-57, and 62-64 is not considered novel in the sense of Article 33(2) PCT.

V.2.4 With respect to claims 44-52, and 65-81

None of the documents cited in the international search report describe a method of identifying or characterizing a compound for the treatment or prevention of pain comprising the determination of the intracellular chloride level and a method for diagnosing or prognosticating pain associated with CNS dysfunction comprising the determination of the intracellular chloride level. Therefore, the subject-matter of claims 44-52 and 65-81 is considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)**V.3.1 With respect to claims 44-52 and 65-81**

None of the documents cited in the international search report suggest that the determination of the intracellular chloride level might be the basis of the identification of compounds being beneficial in pain treatment or diagnosis. Therefore, the subject-matter of claims 44-52 and 65-81 is considered inventive in the sense of Article 33(3) PCT.

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International application No.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

PCT/CA2004/000726

V.4 Industrial applicability (Article 33(4) PCT)**V.4.1 With respect to claims 1-23 and 25**

The subject-matter of claims 22-30, 32, 34, 44-52 appears to be susceptible of industrial application.

V.4.2 With respect to claims 1-21, 31, 33, 35-43, 53-81

The subject-matter of claims 1-21, 31, 33, 35-43, 53-81 is considered to be a method of treatment by therapy of the human or animal body and/or a diagnostic method practised on the human/animal body.

For the assessment of the present claims 1-21, 31, 33, 35-43, 53-81 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.5 Further remarks**V.5.1 With respect to claim 3**

The abbreviation "KCC2" used in the claims should be spelled out at least once, e.g. in claim 3, in order to avoid a lack of clarity (Article 6 PCT).

V.5.2 With respect to claims 21 and 64

The term "substantially identical" used in claims 21 and 64 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

Item VI**VI.1 With respect to documents D6-D7**

The examination report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the above cited

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/CA2004/000726

documents D6-D7 would be relevant with respect to novelty and inventive step (Article 33(2) and (3) PCT). Furthermore, should the present application be entered into the regional phase, the document D6 could be relevant to the question of novelty.